REMARKS

Reconsideration is requested.

Claims 15-32 and 34 are pending.

Rejoinder and allowance of the withdrawn claims with the claims under active consideration are requested. The Examiner is requested to appreciate in this regard that claims 18-27 define methods which require and are dependent from the methods of the claims under current examination, with additional method steps. Claims 18-27 therefore, at a minimum, are believed to be properly rejoined and allowed with the claims under active consideration.

Claim 16 has been amended above to recite language consistent with claim 15, from which claim 16 depends. No new matter has been added. The amendment does not raise new issues requiring further search and/or consideration. Entry of the Amendment is requested.

The Section 102 rejection of claims 15 and 16 over McDonough (EP 0569237A2) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The cited art to relates to a method to detect whether a sample comprises HBV. Probes are disclosed to detect unique sequences in the HBV genome which are capable to distinguish between the HBV and its known phylogenetic neighbors, see the summary of the invention.

Page 1, lines 9-20 of the present application describes the following:

> Hepatitis B virus is a small enveloped DNA virus of approximately 3200 bp long. Historically it has been

> characterized on the basis of immunological reaction of the HBsAg with sets of monoclonal antibodies. Isolates were described as *a*, indicating the common determinant for all different subtypes, followed by subtype-specific combinations: *dw, dr, yw*, or *yr*. The latter are mutually exclusive pairs of determinants, covering the HBsAg amino acids 122 (d = lys, y = arg) and 160 (w = lys, r = arg)- Several subdeterminants for w exist and can be ascribed t o the appeareance [sic] of certain amino acid variants at codon 127. More recently, a genetic classification has been proposed, based on molecular analysis of the virus. This kind of analysis showed that in total six different genotypes exist, indicated from A to F, with a maximum genetic divergence of 8% when ,comparing complete genornes (reviewed by Magnius and Norder, 1995).

The present specification therefore describes the well known definitions of subtypes *adw*, *adr*, *ayw* and *ayr* characterized as having amino acid variations in the HBsAg amino acids 122 and 160, wherein

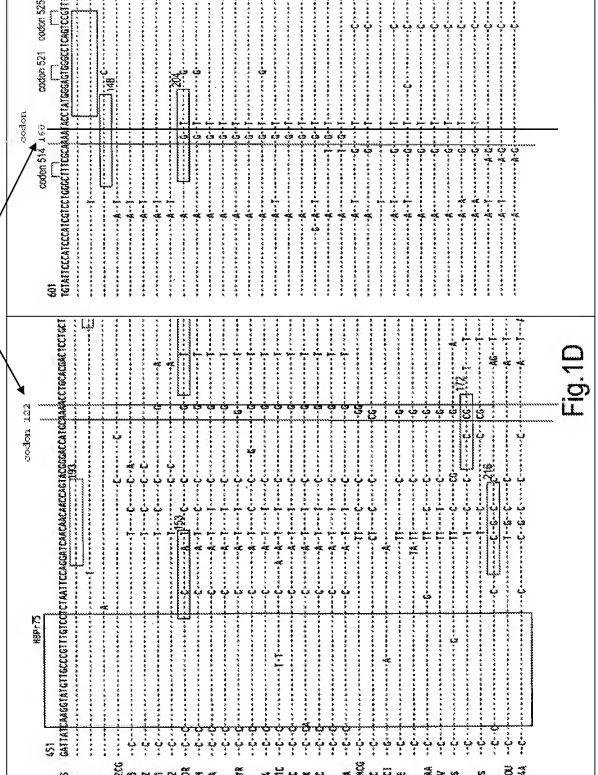
subtype *adw* has a lysine (encoded by AAA or AAG) at codons 122 and 160;

subtype *adr* has a lysine (encoded by AAA or AAG) at codons 122 and an arginine (encoded by AGA or AGG) at codon 160;

subtype *ayw* has an arginine (encoded by AGA, AGG or CGA) at codons 122 and a lysine (encoded by AAA or AAG) at codon 160; and

subtype *ayr* has an arginine (encoded by AGA or AGG) at codons 122 and 160.

The present application further describes, for example, in Figure 1, sequences of genotypes A-F. An annotated reproduction of Figures 1D and 1E is provided as follows wherein codons 122 and 160 are highlighted and the subtype of each sequence is labeled in the left margin based on the above-quoted disclosure of the present specification:


codon 122
codon 514
codon 521
codon 525
codon 528
Fig.1D
Fig.1E

The applicants note that in the above, sequences HBVXCPS, HBVADW, HVHEPB, S50225, and HPBADWZCG, are genotype A sequences; sequences HPBADW3, HPBADWZ, HPBADW1, and HPBADW2, are genotype B sequences; sequences HPBCGADR, HBVADRM, HPBADRA, HPBCG, HEHBVAYR, HBVADR, HBVADR4, HPBADR1C, HPBADRC, HBVPREX, HPBETNC, HHVBC, and HHVCCHA, are genotype C sequences; sequences HBVAYWMCG, HBVAYWC, HBVAYWCI, HBVAYWE, HBVDNA, HPBHBVAA, XXHEPAV, and HBVORFS are genotype D sequences; sequences HHVBE4 and HHVBBAS are genotype E sequences; and sequences HHBF, HHVBFFOU, and HBVADW4A are genotype F sequences.

The Examiner is urged to appreciate that Figures 1D and 1E illustrate that detecting subtype *adw* of HBV will not specifically detect genotype A, as required by the pending claims. Specifically, as subtype *adw* of HBV may be found in at least genotypes A, B, D and F of the samples of Figures 1D and 1E of the present specification, a method and materials for detecting serotype *adw* of HBV, such as is described in the cited art, will not necessarily provide a method or materials for determining the presence or absence of HBV genotype A in a biological sample, as required by the pending claims.

The claims are submitted to be patentable over the cited EP 569237 and withdrawal of the Section 102 rejection of claims 15 and 16 over the same is requested.

For completeness, the applicants note that the "*a*" of the subtype designation relates to the immunodominant "a" region of the HBV surface antigen (HBsAg).

The *dw* subtype of HBV has been characterized by a lysine on both HBsAg codon 122 and 160, encoded by AAA and AAG. Figures 1D and 1E of the present

patent application exemplify that HBV strains of genotype A, four strains of genotype B, one out of eight strains of genotype D and the three strains of genotype F belong to the *adw* subtype. The HBV strains of genotype C except of one, HEHBVAYR, belong to the *adr* subtype, this adr subtype being characterized by a lysine on HBsAg codon 122, encoded by AAG and an arginine on HBsAg codon 160, encoded by AGA or AGG. The HEHBVAYR strain of the genotype C belongs to the *ayr* serotype characterized by an arginine on both HBsAg codons 122 and 160, encoded by AGA. The strains of genotype E and seven HBV strains genotype D, except for strain HBVAYWC1 belong to the *ayw* subtype characterized by arginine on HBsAg codon 122, encoded by AGA, AGG and CGA, and a lysine on HBsAg codon 160, encoded by AAA. Genotype D strain HBVAYWC1 belongs again to the *adw* subtype.

The present specification therefore demonstrates that the classification in immunological subtype-specific combinations *dw, dr, yw* and *yr* is distinct from the genetic classification based on molecular analysis. Therefore, the HBV genotype A is a subgroup of HBV different from the *adw* subgroup to which group strains of the genetic type B, D and F belong.

A method to detect specifically the *adw* subtype is not suitable to, and will not necessarily, detect the genotype A or any other specific genotype.

Accordingly, even if EP 569237 discloses a method to specifically detect the HBV *adw* subtype strains, this method could not be used for the specific detection of genotype A strain, as required by the presently rejected claims.

Withdrawal of the Section 102 rejection is requested.

Again, for completeness, the applicants note that EP 567237 describes three probes on the second page (SEQ ID NO 2 and 3) which are part of the Hb polymerase gene, see nucleotides 1523-1544 of FIG 1K of the present application at the end of the HB pol protein and nucleotides 2368 – 2394 of FIG 1P of the present application at the start of the HB pol protein. SEQ ID NO 1 of the cited art could not be located in the referenced article from Nucleic Acids Research. This method disclosed in EP 567237 is essentially different from the present invention which discloses a method to detect in a sample the presence or absence of a well-defined genotype HBV genotype A by applying a probe of the HBsAg region.

Withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claims 15-17, 28 and 29 over McDonough, Maertens (WO 94/12670) and Ashton-Rickard (Journal Medical Virology 1989, November; 29(3); 196-203), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The secondary references fail to cure the deficiencies of the primary reference noted above.

The Examiner is understood to believe that Ashton-Rickard teaches that a determine region of HBV genotype A is located between amino acid residues 138 – 147. However, in this article there is no mention of any genotype, and therefore also not about genotype A. The reference is believed to relate to the HBsAg region and not to a (A) genotype.

WO 94/12670 does teach a method for determining the type or subtype of HCV and mentions the possibility of the application of probes to detect different HB surface

antigen or core antigen or precore antigen mutants. In this patent application there is no mention of the detection of HBV genotype A and no HBV probe or primer is mentioned relating to the same.

As described above, EP 569237 describes a method to detect whether a sample comprises HBV. Probes have been disclosed to detect unique sequences in the HBV genome which are capable to distinguish between the HBV and its known phylogenetic neighbors.

The claimed invention would not have been obvious from the combination of cited art. Withdrawal of the Section 103 rejection is requested.

Rejoinder of previously-withdrawn subject matter and allowance of same with the pending active claims are requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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